CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	NDA 21-310	**Application Type:**	NDA
Sponsor:	Watson Laboratories	**Proprietary Name:**	Alora
Pharmaceutical Category:	Estrogen	**Route of Administration:**	Transdermal
Indication:	Prevention of Postmenopausal Osteoporosis	**Dosage:**	0.025 mg/day, 0.050 mg/day, 0.075 mg/day
Reviewer:	Patricia Beaston-Wimmer, M.D., Ph.D.	**Date Review Completed:**	October 10, 2001

Chemistry Reviewer: Elsbeth Chikhale, Ph.D.

Pharmacology Reviewer: Karen Davis-Bruno, Ph.D.

Biopharmaceutics Reviewer: Wei Qiu, Ph.D.

Statistical Reviewer: Todd Sahlroot, Ph.D.

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____	**Not Approvable**
	X	**Approve**		

SIGNATURES: Medical Reviewer: Patricia Beaston-Wimmer, M.D., Ph.D.

Medical Team Leader: Eric Colman, M.D.

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Executive Summary

I. Recommendations

Watson Laboratories has submitted the results of one clinical study to support the new indication, prevention of postmenopausal osteoporosis, for Alora (transdermal estradiol). The data support the indication for the currently approved doses 0.050, and 0.075 mg/day and a new dose, 0.025 mg/day. This reviewer recommends approval of the new indication for the above doses. Recommendations regarding labeling changes are found in the Appendix. There are no recommendations for Phase 4 Studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Alora, transdermal estrogen, has been approved for the treatment of postmenopausal symptoms related to estrogen deficiency. Watson seeks approval for a new indication, prevention of postmenopausal osteoporosis. This submission contains data from one 2-year clinical trial in which 355 patients were randomized to 3 doses of estrogen and placebo.

B. Efficacy

This study compared the effect of three doses (0.025, 0.050, 0.75 mg/day) of estrogen to placebo on the change in lumbar spine bone mineral density (LS BMD) over a 2-year period in postmenopausal women with a history of hysterectomy. The primary measure of efficacy was mean percent change in LS BMD from baseline to exit. There was a statistically significantly larger mean percent change for the 0.025, 0.05, and 0.75 doses of estrogen (1.65, 4.08, 4.82%, respectively) compared to placebo (-0.59 %). Although across study comparisons of efficacy cannot be made easily because of dissimilarities in patient populations enrolled, in general, the efficacy of Alora was similar to other approved estrogens.

C. Safety

Three-hundred and fifty-five (355) patients were randomized to the study. Safety analyses included all subjects who received at least one dose of stud drug. The mean duration of exposure was 495.6 days (median 722, range 4 to 785). The most common side effects included breast pain and hypertension — events consistent with estrogens as a class. Since the patients in this study all had a history of hysterectomy there are no data on the effects of Alora on the endometrium nor are there data regarding the use of Alora with a progestational agent. Application site reactions were reported in 55.8% of participants with similar frequency across groups. In comparison, the incidence of application site reactions reported for another transdermal estrogen (Vivelle) was 8.5%.

Safety labs and mammography were appropriately planned in the study. Although mammography provided useful screening and follow-up data for breast cancer, the relatively short duration and small sample size of the study do not lend themselves to an accurate assessment of breast cancer risk. There is no reason, however, to believe that an Alora associated risk for developing breast cancer would be different than that observed with other estrogens.

A potential drug-drug interaction was overlooked in this study. Current labeling for estrogens discuss the increase in thyroid binding globulin (TBG) observed in patients initiating estrogen therapy but states that 'free T_4 and free T_3 concentrations are unaltered. This is true only for those patients with an intact thyroid axis. Patients who are dependent on exogenous thyroid hormone cannot increase thyroid hormone production in response to increased TBG and are at risk of under treatment. There was no provision for monitoring patients on thyroid hormone treatment in this study. (Changes to the label have been suggested in the Appendix on labeling changes.)

D. Dosing

A 'no effect' dose has not been established. The lowest dose used in this study (25 mcg) gave similar efficacy relative to placebo as that seen with that same dose of Vivelle, another transdermal estrogen. While statistically significant, this low dose provided a relatively small improvement in BMD over the time studied (2 years). Because fracture data for estrogens are not required for approval and there are no long term data available for this lower dose, it would be difficult to argue that pursuing a lower dose would provide adequate efficacy.

The relationship of adverse events to dose of estrogen are well described. They include breast tenderness and increased risk of endometrial cancer, breast cancer and deep vein thrombosis with higher doses. While a lower dose (0.025mg/d) has demonstrated efficacy for the prevention of PMO, it may be less efficacious for the treatment of vasomotor instability, Those adverse events that are dependent on the hepatic 'first-pass effect' such as increased triglycerides appear to be attenuated by transdermal delivery.

[redacted]

E. Special Populations

Alora is indicated for use by postmenopausal women and therefore not indicated for use in males, children (a pediatric waiver was requested) or pregnant women.

The majority (86.5%) of the subjects in this study were white. Osteoporosis is generally a condition of thin, white or Asian women. There is insufficient clinical information available to make recommendations for other populations.

The safety and effectiveness in geriatric patients (over age 65) have not been established (current labeling). Estrogens are prescribed to many patients in this age group for prevention and treatment of osteoporosis. While some patients enrolled in this study were ≥ 65 years of age, the study was not designed to specifically address safety and efficacy in this population.

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Clinical Review[*]

I. Introduction and Background

Postmenopausal osteoporosis (PMO) is a common disorder and has been well described. It is characterized by an accelerated bone turnover in the first six months after estrogen deprivation, natural or surgical. After the initial 6-months the rate of turnover slows and plateaus. An imbalance in destruction and production of bone results in decreased bone mass and loss of bone microarchitecture. The remaining bone demonstrates normal histology without evidence of osteomalacia. Hormone replacement therapy (HRT) has been shown to prevent the rapid increase in turnover and to preserve bone mineral density. In addition to HRT modification of risk factors for osteoporosis are recommended. These include weight bearing exercise, adequate intake of calcium and Vitamin D, cessation of tobacco use and moderate caffeine intake, and maintenance of a reasonable body weight.

A number of estrogen products, oral and transdermal, are in use for the prevention of PMO. In general no difference in efficacy has been demonstrated for this indication between the two approved routes of administration. The transdermal route avoids the 'first pass effect' of the liver resulting in less metabolism of estradiol to estrone. The clinical significance of increased estradiol delivery has not been established, but the hypertriglyceridemia observed in some patients taking oral estrogens is not seen with transdermal estradiol use. Because estrogen treatment is associated with increased risk of breast cancer, endometrial cancer and venous thrombosis, companies have attempted to identify the 'lowest effective dose'.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Alora, 17ß-estradiol transdermal system, was approved by DRUDP in December 1996 (NDA 20-655) for the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval and vaginal atrophy, and treatment of hypogonadism, castration, or primary ovarian failure. The currently approved doses are 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. Watson is seeking a new indication of "prevention [redacted] of postmenopausal osteoporosis" for the currently approved doses and a new dose, 0.025 mg/day.

B. State of Armamentarium for Indication

Currently approved drugs for prevention and treatment of osteoporosis are limited to therapies that decrease bone resorption and include 1) other estrogen products and the selective estrogen receptor modifier (SERM) raloxifene, 2) bisphosphonates, and 3) calcitonin. Calcium and Vitamin D supplementation are recommended to postmenopausal women as part of good clinical practice. To date no therapies have been approved that promote bone formation.

[*] Direct quotes from the NDA submission are *italicized*, Reviewer's comments are **bolded**.

C. Important Milestones in Product Development

FDA Agreements

April 1, 1996 – The Divisions (DMEDP and DRUDP) concurred that inclusion of only hysterectomized women would be acceptable in the osteoporosis study. The labeling would reflect that the clinical study was performed solely on this patient population. Additionally, an osteoporosis claim could be obtained [redacted] if estrogen equivalence with their estradiol patch could be demonstrated.

June 27, 1996 – Statistical analysis plan for the Phase III study would include a last observation carried forward analysis.

July 31, 1996 – The Divisions agreed that measurement of trabecular bone density in lumbar bone rather than cortical bone density in the hip would be appropriated as long as the product labeling disclosed this as the primary study endpoint. Consistent with the current guideline for development of products for osteoporosis , the Divisions recommended a washout period of six months from prior estrogen treatment be incorporated into the study design because of the effects of prior estrogen treatment on bone marrow density. [redacted]

May 20, 1997 – DRUDP approved the Watson's request to shorten the washout period from previous estrogen therapy from 6 months to 2 months. (Additional changes in the inclusion and exclusion criteria are noted in the section describing the study population.)

The Divisions concurred that conclusions reached in the hysterectomized patient population could be extrapolated to non-hysterectomized women.

If the 0.025 mg/day dose was determined to be effective, the higher strengths of Alora [redacted] would still be approved for vasomotor symptoms but the product labeling would need to address the finding of a lower effective dose for postmenopausal osteoporosis.

Formulation Change

Watson changed [redacted] It appears from the records that the 'old' formulation was used for the lowest dose studied, 0.025 mg. There is no documentation regarding the formulation used of the other doses employed in the study. DRUDP approved the use of the new formulation for the 0.05, 0.075, and 0.100 mg/day doses. The biopharmaceutic review from DRUDP was reviewed. There was an approximately 95% bioequivalence between the new and old formulations using the 18 cm^2 system. Since the 9 cm^2 system uses the same formulation at half the size a similar bioequivalence would be expected.

[redacted]

Prior FDA reviews of Alora

1) NDA 20-6— Sponsor TheraTech, Inc., Division DRUDP, Review Date 11/14/96.
2) NDA 20-655/S-002, Sponsor TheraTech, Inc., Division DRUDP, Review Date 10/15/97Biopharmaceutic and adhesion comparison [redacted]

D. Other Relevant Information

Trade Secret [redacted]

The trial that is the subject of this review was started by Proctor and Gamble Pharmaceuticals and transferred to Watson Laboratories, Inc.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Per Chemistry reviews (initial and current NDAs). According to Chemistry, [redacted] changed from the time of the initial approval and completion of the study in this NDA. The formulation used with the individual patients in this study is not recorded in the data base provided. The new formulation has been evaluated by DRUDP and was approved. Additional information regarding the lower dose is found in the chemistry review for this NDA.

III. Human Pharmacokinetics (PK) and Pharmacodynamics (PD)

Per PK/PD reviews (initial and current NDAs). According to Pharmacokinetics, information regarding the change [redacted] was submitted to DRUDP. The drug delivery based on drug depletion was within the acceptable range. Additional information regarding the lower dose are found in the PK/PD Review for this NDA.

IV. Description of Clinical Data and Sources

This submission consisted of 38 paper volumes and an electronic data set. The results of one clinical trial were provided. Alora has been marketed since December 1996. Forty-two (42) adverse events were recorded in the AERS system (as of 8/31/01) and were generally consistent

with estrogens as a class. .There is an extensive literature on estrogens and postmenopausal osteoporosis, including the data obtained in the more recently completed HERS study.

V. Clinical Review Methods

A. Evaluation of Material Submitted

All submitted information was reviewed. Both efficacy data and safety data were confirmed or recalculated using the electronic data set included with the submission. The quality and organization of the data set provided were poor. While the quality of the data set made the data confirmation process time consuming, it did not prevent review of the major components of the submission. Previous reviews and current labels for this and other approved estrogens were also reviewed.

B. Evaluation of Financial Disclosure

Watson has provided the names of 25 primary investigators and 147 sub-investigators. Disclosure of financial interests was provided [redacted]

VI. Review of Efficacy

A. General Approach to Review of the Efficacy

In order to demonstrate efficacy of an estrogen in the prevention of PMO, the Guidance for Evaluation of Drugs for Osteoporosis requires demonstration that drug-treated subjects have a mean increase in BMD that is statistically significantly greater than the change in placebo-treated subjects. (This is in contrast to non-estrogen drugs for which fracture prevention data are required.) Watson has demonstrated statistically significant efficacy in preserving or improving BMD in postmenopausal women for all estrogen doses tested when compared to placebo. However, based on the trial design, there are limitations to the claims that can be made in the label. These difference are noted on the annotated version of the label.(see Appendix)

B. Detailed Review of Trial

This submission consisted of a single study.

Clinical Study

Title: A randomized, parallel-group, double blind, double-dummy, placebo-controlled, multi-center, Phase III, dose-ranging study of 24 months (26 cycles of 28 days each) duration in postmenopausal women who have had a hysterectomy.

Objective: The objective was to establish the minimally effective estradiol dose that significantly prevents lumbar spine bone loss, as measure by bone mineral density (BMD), when compared to placebo.

Study Design:

Patient Population:

Inclusion Criteria

Female <70 years old at baseline visit (Protocol Amendment 1, Change 2);

Had a hysterectomy with or without bilateral oophorectomy and FSH value >40 mIU/ml plus serum estradiol <20 pg/ml as adequate documentation of menopausal status. Surgical menopause (documented bilateral oophorectomy) must be at least 12 months before starting study drug. [An estradiol level of 23 pg/ml or less (based on the assay precision of ——, without regard to the FSH level, was used as hormonal definition of menopause as documented in a Protocol Amendment].

Had documented normal TSH value at screening, if subject was taking thyroid replacement therapy;

Had a normal screening mammogram (documented results of a normal mammogram within 6 months was acceptable);

Agreed to take estrogen for the 2-year study duration;

Had a lumbar spine bone mineral density (BMD) by — >0.722 g/cm^2 on a —— scanner, or >0.882 g/cm^2 on the —— machine; **(These values correspond to a T-score ≥ -2.5.)**

Was ambulatory; and

Was able and willing to participate in the study as evidenced by providing written informed consent.

Exclusion Criteria

Had a history of intolerance to estrogen or related compounds, or had a known or suspected hypersensitivity to any constituents of transdermal systems;

Received oral estrogen therapy within the past 2 months including phytoestrogens (Protocol Amendment, Change 1);

Had evidence of clinically significant organic disease on history or physical examination that, in

the opinion of the Investigator and/or P&GP Protocol Physician, would prevent the subject from completing the study;

Had evidence of a clinically significant psychiatric disorder, e.g., major depression, etc., on history or physical examination which, in the opinion of the Investigator and/or P&GP Protocol Physician, would prevent the subject from completing the study;

Had a history of cancer with the exception of:
Basal cell carcinoma with a documented 6-month remission,
Carcinoma in situ of the uterus or cervix treated by hysterectomy;

Had a history of hyperparathyroidism, untreated hyperthyroidism, or osteomalacia within 1 year before starting study drug;

Had contraindications to estrogen use as determined by a history of:
Carcinoma of the breast,
Estrogen dependent neoplasia,
Thrombophlebitis,
Thromboembolic disorders;

Had abnormal laboratory parameters at screening including:
Hemoglobin A1c > 10% of the upper limit of normal,
*Fasting serum total cholesterol, LDL, and triglycerides > 25% above the upper limit of normal,
*Fasting serum HDL > 20% below the lower limit of normal,
(*removed lipid levels as exclusionary criteria, Amendment1, Change 4)
Serum creatinine > 2 mg/dl,
ALT or AST results > 1.5 times the upper limit of normal,
Bilirubin results > 2 times the upper limit of normal.

Had a history of using the following medications within 3 months of starting study drug or for more than 1 month within the last 6 months before study drug:
> 400 µg/day of inhaled beclomethasone or equivalent,
Oral or parenteral glucocorticoids (≥5 mg prednisone or equivalent/day),
Anabolic steroids,
Calcitonin,
Vitamin D supplements (>800 IU/day) orally,
Calcitriol;

Had a history of using any of the following medications within 3 months of starting study drug:
Any bisphosphonate,
Fluoride (>10 mg/day);

Participated in another clinical study involving active intervention within 30 days prior to start of dosing in this study;

Had abnormalities on the AP or lateral lumbar radiographs such as severe scoliosis (>15 to 20 degrees depending on the degree of associated osteophytosis), spinal fusion, aortic calcification, or severe fracture deformation that would preclude precise measurements as determined by the radiographic screening facility. At least 2 lumbar vertebrae (LI-L4) in the scanning field must be without fracture for analysis; or

Had physical characteristics (such as body and girth) which would preclude precise measurements as evidenced by review of the baseline by the Investigator.

Comment: The inclusion/exclusion criteria are generally reasonable and approximate the criteria in the guidance for the study of estrogen for the prevention of postmenopausal osteoporosis. The majority of the variations from the guidance were agreed on as noted. However, the inclusion/exclusion criteria allow for enrollment of patients who would not be considered to have risk factors for developing postmenopausal osteoporosis, this will be discussed further in the description of the study population. There is no record regarding the recruitment process for this study or by what criteria potential patients failed to meet the criteria of the study. Additionally, there was no description of the methods used to confirm that patients did not have 'untreated hyperthyroidism', hyperparathyroidism or abnormalities of Vitamin D regulation. It is important for prescribing physicians to have data demonstrating how study populations compare to the general population to make clinical judgements for treating individual patients.

Study Medications:

Four treatment groups. Double-Dummy approach:

Alora 0.025 mg/day (9cm^2 system) and placebo (18 cm^2 system)
Alora 0.050 mg/day (18cm^2 system) and placebo (9 cm^2 system)
Alora 0.075 mg/day (9cm^2 and 18 cm^2 systems)
Placebo (9cm^2 and 18 cm^2 systems)

Subjects were randomized to one of four treatment groups. A treatment regimen was defined as the application of 2 systems, one 9cm^2 and one 18 cm^2 to the same side of the abdomen every 3.5 days. The commercial Alora product is approved for twice weekly applications. The system application sites were alternated form the left to the right side of the abdomen every 3.5 days. A subject was instructed to allow 1 week between applications of systems to a particular site.

Comment: The doses used in this study represent the attempt to identify the lowest efficacious dose to limit adverse events related to estrogen exposure.

All patients received 1000 mg of oral elemental calcium in the form of 2 OsCal tablets daily.

Comment: It is recommended that postmenopausal women have a 1500 mg daily intake of elemental calcium and supplemental Vitamin D of 400-800 IU daily. The 1000 mg of oral calcium given to study patients is probably adequate; there was no Vitamin D given in this study. Review of the concomitant medications revealed that a number of patients used vitamin and herbal supplements. The data structure makes it difficult to determine the distribution of patients taking supplements (those containing calcium and/or Vitamin D) that might affect BMD. Vitamin D levels were not obtained at screening to rule out deficiency nor was Vitamin D supplemented during the study. Patients who might have been Vitamin D deficient prior to the study may have benefited (by increase in BMD) by taking Vitamin D or Vitamin D containing supplements after the study had started.

Efficacy Assessments

Primary efficacy parameter: *The mean percentage change from baseline in lumbar spine BMD at the end of 2 years.*

Secondary efficacy parameters: *The percent change from baseline in lumbar spine BMD at Cycle 13, and the actual change from baseline in lumbar spine BMD at Cycle 13 (1-year) and Cycle 26 (2-years).*

BMD measurements were obtained on either [redacted] machines. The [redacted] were evaluated at a central facility, [redacted] The machines provide different BMD measurements. In order to make the baseline readings from the machines comparable, raw BMD measurements were standardized using the following algorithm:

standardized BMD = 1.0755 x BMD [redacted]
= 0.9522 x BMD [redacted]

Comment: According to the protocol submitted, radiographs of the lumbar spine were to be performed at both the screening and Cycle 26 (or exit) visit to *ensure the integrity of the lumbar area being assessed by* [redacted] In the electronic data base only information on radiographs at exit are provided. Watson was contacted to obtain information regarding radiographs from screening. Waston stated that the information in the data base represented screening radiographs and that exit radiographs were not performed. This issue was clarified in attempts to correctly identify the intent to treat population and for information regarding vertebral fractures.

Although [redacted] were obtained at the end of the first year of treatment (Cycle 13), there did not appear to be safety escape criteria for excessive bone loss.

Statistical Analysis

An overall analysis of variance (ANOVA) method was used to compare the treatment groups with respect to the primary efficacy parameter. A total of approximately 336 subjects were to be recruited. Each treatment group was to be allocated approximately 84 subjects. Assuming a 50% drop out rate by the end of 2 years, 42 subjects per treatment group were expected to complete the study. This sample size provided 90% power to detect a 5% difference (standard deviation = 7%) between an active estrogen arm and placebo in the rate of bone loss based on 2-sample t-test at the 0.05 significance level. A full discussion of the statistical analysis can be found in the Biometrics review by Dr. Sahlroot.

Study Schedule

The following is a tabular summary of the trial procedures and schedule. Details regarding specific safety and efficacy parameters are discussed in the appropriate sections.

STUDY SCHEDULE	CYCLE												
Procedure	Screen	Baseline	1	2	3	5	7	10	13	16	20	23	26*
Informed Consent	✓												
Personal and Demographic Data	✓												
Medical and Drug History	✓												
Physical, Breast & Pelvis Exams	✓						✓		✓		✓		✓
Mammogram (or report if < 6 months)	✓								✓				✓
FSH and Estradiol	✓												
AP & Lateral Lumbar Radiograph	✓												
— - Lumbar spine	✓								✓				✓
Hematology	✓						✓		✓		✓		✓
Serum Chemistry	✓						✓		✓		✓		✓
Carbohydrate Metabolism	✓						✓		✓		✓		✓
Serum Lipid Profile (TC/HDL/LDL/TG)	✓						✓		✓		✓		✓
Coagulation Profile (PT, PTT)	✓						✓		✓		✓		
Serum Hormone Levels (E2, E1)		✓							✓		✓		
Concomitant Medications	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Vitals Signs	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
EKG		✓											
Dispense Study Drug		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Dispense Calcium		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Study Medication Compliance Check			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Assessment			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Telephone Contact				✓									
Lateral Lumbar Radiograph													✓

*All procedures listed at Cycle 26 should be carried out at the patient's exit visit if the patient discontinues at an earlier visit.

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Results

Population Demographics

The study population enrolled is described in the table below.

Parameter	Estradiol 0.025 mg/day (N=89)		Estradiol 0.050 mg/day (N=90)		Estradiol 0.075 mg/day (N=89)		Placebo (N=87)		Overall (N=355)	
Age (years)										
Mean ± SE	51.6 ± 0.9		53.7 ± 0.7		54.0 ± 0.7		53.8 ± 0.7		53.2 ± 0.4	
Median	52		53		54		54		54	
Range	29-69		30-69		36-69		26-68		26-69	
Weight (lbs)										
Mean ± SE	171.2 ± 4.0		165.9 ± 3.58		169.6 ± 3.79		161.8 ± 3.36		167.2 ± 1.9	
Median	164		162.5		165		160.5		162.5	
Range	94.5-281.0		100.0-255.0		103.0-307.0		100.1-262.8		94.5-307.0	
Height (ins)										
Mean ± SE	64.6 ± 0.3		64.1 ± 0.2		64.4 ± 0.3		64.4 ± 0.3		64.3 ± 0.1	
Median	64.5		64.2		64.5		64.5		64.5	
Range	57.0-70.0		59.5-69.0		59.0-70.0		59.5-68.8		57.0-70.0	
BMI (kg/m^2)*										
Mean ± SE	29.2 ± 0.7		28.5 ± 0.6		28.9 ± 0.6		27.5 ± 0.5		28.5 ± 0.3	
Median	27.9		28.2		27.6		27.1		27.6	
Range	15.2-48.5		16.9-43.3		18.0-48.7		17.2-41.3		15.2-48.7	
Yrs since hysterectomy			89							
Mean ± SE	15.7 ± 0.93		15.6 ± 0.76		16.9 ± 0.89		16.2 ± 0.92		16.1 ± 0.44	
Median	16.6		16.0		17.0		16.4		16.5	
Range	0.7-36.8		1.2-33.6		1.1-36.1		0.8-36.4		0.7-36.8	
L-Spine T-Score			89							
Mean ± SE	-0.69 ± 0.12		-0.47 ± 0.13		-0.72 ± 0.12		-0.68 ± 0.12		-0.64 ± 0.06	
Median	-0.80		-0.60		-0.80		-0.80		-0.75	
Range	-2.5-3.3		-2.7-3.2		-2.6-3.8		-2.5-3.6		-2.7-3.8	
	n	%	n	%	n	%	n	%	n	%
Race										
Caucasian	78	87.6	76	84.4	79	88.8	74	85.1	307	86.5
Black	6	6.7	7	7.8	6	6.7	6	6.9	25	7.0
Hispanic	3	3.4	4	4.4	1	1.1	5	5.7	13	3.7
Other	2	2.2	3	3.3	3	3.4	2	2.3	10	2.8
Tobacco Use										
Never Used	35	39.3	51	56.7	36	40.4	41	47.1	163	45.9
Previously Used	26	29.2	23	25.6	28	31.5	24	27.6	101	28.5
Currently Used	28	31.5	16	17.8	25	28.1	22	25.3	91	25.6
Alcohol Use										
Never Used	19	21.3	23	25.6	25	28.1	22	25.3	89	25.1
Previously Used	13	14.6	8	8.9	14	15.7	5	5.7	40	11.3
Currently Used	57	64.0	59	65.6	50	56.2	60	69.0	226	63.7
Estrogen Use										
Never Used	75	84.3	72	80.0	76	85.4	72	82.8	295	83.1
Previously Used	14	15.7	18	20.0	13	14.6	15	17.2	60	16.9

Statistics: Pairwise comparisons were made between each treatment group and placebo. There were no statistical differences between groups for the above parameters.
*BMI data generated by this reviewer using the data base provided.
All patients are from the USA.

The mean age at hysterectomy was 37.1 years (range 19-62). The mean time since hysterectomy was 16.1 years (range 0.7-36.8). At baseline, the mean estradiol level was 3.4 pg/ml (range 0-112), and mean FSH level was 66.3 IU/l (range 4-171). The mean lumbar spine BMD was 1.051

g/cm^2 (range 0.82-1.56). The mean lumbar spine T-score was –0.64 (range -2.7 to -3.8; 6 subjects had T-score ≤ -2.5, 3 completed the study). There were no statistical differences among the groups for these parameters.

Comment: The time since menopause is not known for the majority of the subjects. The information available in the data set is 'time from hysterectomy' (months and years) and history of oophorectomy (yes or no). One hundred and sixty-nine (169, 47.6%) had no history of oophorectomy. The menopausal status prior to surgery, hysterectomy and oophorectomy, was not reported. Therefore, although Watson provides a number of analyses using time from hysterectomy as a variable, these analyses offer little information because it is not the presence of the uterus but the estrogen status of the patient that influences bone mineral density.

The time from discontinuation of estrogen therapy was not found in the data set. There is accelerated bone loss in the first 6-months after discontinuation of estrogen therapy with a decrease in the rate of loss after that initial period. Failure to equally distribute patients with a 'short time from discontinuation of estrogen' could affect the comparisons among groups. However, the number of patients who received estrogen treatment prior to this trial was relatively small and should not effect the overall findings of the study. Similarly, there was a wide range in time since hysterectomy with the majority (87.6%) of the patients having had a hysterectomy > 5 years prior to enrollment in the study. Therefore the patient population enrolled in this study is more likely to have completed the rapid turnover phase of the early postmenopausal state and would give less information regarding prevention.

Mean BMI was 28.5 kg/m^2 (median 27.6, range 15.17 to 48.69) and was similar across groups. In general, obese women are not considered to be at risk for developing PMO because of higher circulating estrogens, principally estrone (which is formed by peripheral aromatization of androstenedione). With the exception of a tobacco use history, there was little evaluation of other osteoporosis risk factors in this study population making it difficult to determine if these overweight and obese patients would have been at risk for developing PMO.

Subject Disposition

A total of 355 patients were enrolled in the study. The following tables summarize the patient disposition by treatment and the reasons for premature termination.

Subject Disposition	Estradiol 0.025 mg/day		Estradiol 0.050 mg/day		Estradiol 0.075 mg/day		Placebo		Overall	
	n	%	n	%	n	%	n	%	n	%
Randomized	89	100.0	90	100.0	89	100.0	87	100.0	355	100.0
Completed	44	49.4	49	54.4	45	50.6	58	66.7	196	55.2
Premature Termination	45	50.6	41	45.6	44	49.4	29	33.3	159	44.8
≥ 1 follow-up BMD	60	67.4	64	71.1	63	70.8	72	82.8	259	73.0

Reason for Termination	Estradiol 0.025 mg/day (N=89)		Estradiol 0.050 mg/day (N=90)		Estradiol 0.075 mg/day (N=89)		Placebo (N=87)		Overall (N=355)	
	n	%	n	%	n	%	n	%	n	%
Total Premature Terminations	45	50.6	41	45.6	44	49.4	29	33.3	159	44.8
Adverse Event										
Total	14	15.7	12	13.3	20	22.5	6	6.9	52	14.6
Application-Site Reaction	7	7.9	8	8.9	9	10.1	0	0	24	6.8
Investigator Recommendation	1	1.1	2	2.2	0	0	0	0	3	0.8
Protocol Violations										
Total	4	4.5	7	7.8	1	1.1	3	3.4	15	4.2
Inclusion Criteria	0	0	1	1.1	0	0	0	0	1	0.3
Exclusion Criteria	0	0	3	3.3	0	0	1	1.1	4	1.1
Non-Compliance										
Dose Schedule	0	0	0	0	1	1.1	0	0	1	0.3
Visit Schedule	4	4.5	3	3.3	0	0	2	2.3	9	2.5
Excluded Concomitant Medication	1	1.1	0	0	1	1.1	0	0	2	0.6
Voluntary Withdrawal	15	16.9	13	14.4	11	12.4	12	13.8	51	14.4
Lost to Follow-up	8	9.0	7	7.8	11	12.4	8	9.2	34	9.6
Death	2	2.2	0	0	0	0	0	0	2	0.6

N= Number of subjects randomized to each treatment group
n= Number of subjects by reason for premature termination

Comment: Analysis of the data was confused by the reference to the 'Cycle 26' time point, the endpoint of the study. There were no 'Cycle 26' data in the data set provided. All follow-up BMD measurements were included in the 'ExitBMD' set. Only 155 patients completed 26 cycles (728 days) but not all of these patients provided an exit BMD. In order to analyze data based on patients who had completed the study a 'completer population' was defined. Patients were identified in the data set if they were coded as not having terminated the study and they provided an exit BMD. This distinction provided a completer population of 192 (54.1%) patients (0.025 mg/d – 43; 0.050 mg/d – 48; 0.075 mg/d – 45; and placebo – 56). The mean duration of treatment for the completer population was 730 days (range ———). The Biometrics and Medical reviewers defined the completer population for consistency of their analyses.

Of the 355 patients randomized, 44.8% prematurely terminated participation in the study raising concern that the LOC analysis would not adequately represent the 2-year treatment period. For example, it the majority of patients withdrew prior to Cycle 13 (approximately 1 year) but provided an exit BMD, the LOC analysis would represent a shorter treatment time then planned. To examine this possibility a Survival analysis of early discontinuations was performed with the following results: 192 patients (54.1%) completed the study, 223 patients (63%) completed cycle 13, and 258 patients (73%) were included in the LOC analysis. 'Completers' represented 75% of the patients used in the LOC analysis, therefore it is unlikely that the large patient drop out adversely affected the outcome of the analysis. The Biometrics Reviewer examined the effect of 27% of patients not contributing data to the analysis and found the study result to be robust to the missing data (see Biometrics review).

Watson identified 26 patients (7.2%) as major protocol violators (0.025 mg/d – 4; 0.050 mg/d – 9; 0.075 mg/d – 6; and placebo – 7). Violations included 'abnormal TSH level in patients on thyroid therapy' (7), 'lower than acceptable LS-BMD' (7), 'history of cancer' (3), 'deviations in baseline levels of FSH and estradiol (3), 'abnormal mammogram' (2), 'abnormal laboratory values' (2), 'contraindications to estrogen' (1) and 'disallowed medication (1). Abnormal TSH and low BMD accounted for greater than one-half of the major protocol violations. Since hyperthyroidism is associated with increased bone turnover and can therefore affect BMD, all values were reviewed. Of those patients with abnormal TSH levels, only one had a suppressed TSH. The range for the remaining abnormal values was TSH ——— mIU/l. The BMD range for the protocol violators was ———. In general, these protocol violations equally distributed among the treatment groups and were unlikely to affect the outcome of the study. The inclusion of 14 patients with abnormal lumbar spine radiographs at baseline is discussed in the evaluation of efficacy.

Efficacy

Primary efficacy parameter: the percentage change from baseline in lumbar spine BMD at the end of 2 years.

Lumbar Spine BMD (ITT*)	Estradiol 0.025 mg/day n = 59	Estradiol 0.050 mg/day n = 64	Estradiol 0.075 mg/day n = 63	Placebo n = 72
Baseline				
Mean ± SE	1.054 ± 0.017	1.081 ± 0.018	1.027 ± 0.015	1.041 ± 0.016
Range	[redacted]	[redacted]	[redacted]	[redacted]
End-Point (LOC*)				
Mean ± SE	1.069 ± 0.019	1.118 ± 0.020	1.070 ± 0.015	1.032 ± 0.016
Range	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change Baseline to Endpoint				
Mean ± SE	1.45 ± 0.48	3.39 ± 0.42	4.24 ± 0.49	-0.80 ± 0.45
Range	[redacted]	[redacted]	[redacted]	[redacted]
p-value	0.0018	0.0001	0.0001	

p-value vs. placebo; *ITT = intent-to-treat population, LOC = last-observation-carried-forward

Comment: The data presented by Watson for the primary efficacy outcome was represented to be based on an ITT population (245 patients) at Cycle 26. More correctly, the primary efficacy data should be based on the ITT population with the last-observation-carried-forward (LOC). The LOC analysis should include all patients who were randomized and had ≥ 1 follow-up BMD (this would be 259 patients). Watson excluded 14 patients based on lumbar spine radiographs. All 14 of the excluded patients were noted to have radiographic lumbar spine deformities at baseline and should have been excluded at screening. However, these patients received study drug and were followed long enough to have at least one follow-up BMD and should be included in the LOC analysis. One patient (14701160) was noted to have "fusion with hardware" at baseline and had additional back surgery during the study. This patient was excluded from the LOC analysis because the hardware present would significantly interfere with accurate BMD measurements and could skew the data. This reviewer, with the assistance of the Biometrics reviewer, recalculated the efficacy data using an ITT population of 258 patients (data presented in

preceding table). The Biometrics reviewer confirmed that there was no difference in the outcome of the study using this larger patient population.

Secondary efficacy parameters: the percent change from baseline in lumbar spine BMD at Cycle 13, and the actual change from baseline in lumbar spine BMD at Cycle 13 and Cycle 26.

Lumbar Spine BMD Baseline to Cycle 13 (1-year) (ITT*)	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Baseline	n= 59	n= 64	n= 63	n= 72
Mean ± SE	1.054 ± 0.017	1.081 ± 0.018	1.027 ± 0.015	1.041 ± 0.016
Range				
End-Point (LOC* to Cycle 13)	n = 53	n = 54	n = 50	n = 65
Mean ± SE	1.070 ± 0.019	1.114 ± 0.022	1.078 ± 0.017	1.034 ± 0.017
Range				
Percent Change Baseline to Endpoint				
Mean ± SE	1.31 ± 0.39	3.47 ± 0.48	4.22 ± 0.42	-0.29 ± 0.45
Range				
p-value	0.014	0.0001	0.0001	

p-value vs. placebo; *ITT = intent-to-treat population, LOC = last-observation-carried-forward

Actual Change in Lumbar Spine BMD (ITT*)	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Cycle 13 (LOC* to Cycle 13)	n = 53	n = 54	n = 50	n = 65
Mean ± SE	0.014 ± 0.004	0.037 ± 0.005	0.043 ± 0.004	-0.003 ± 0.005
Range				
Cycle 26 (LOC to Cycle 26)	n = 59	n = 64	n = 63	n = 72
Mean ± SE	0.016 ± 0.005	0.037 ± 0.005	0.043 ± 0.005	-0.009 ± 0.005
Range				

*ITT = intent-to-treat population, LOC = last-observation-carried-forward

Lumbar Spine BMD Completer Analysis*	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Baseline	n = 43	n = 48	n = 45	n = 56
Mean ± SE	1.053 ± 0.021	1.083 ± 0.022	1.046 ± 0.017	1.038 ± 0.018
Range				
Cycle 13 (1-year)	n = 42	n = 47	n = 45	n = 56
Mean ± SE	1.071 ± 0.022	1.119 ± 0.023	1.090 ± 0.017	1.038 ± 0.018
Range				
Percent Change Baseline Cycle 13 (1-year)	n = 42	n = 47	n = 45	n = 56
Mean ± SE	1.59 ± 0.41	3.54 ± 0.49	4.31 ± 0.45	0.04 ± 0.48
Range				
p-value	0.040	0.0001	0.0001	
Cycle 26 (2-years)	n = 43	n = 48	n = 45	n = 56
Mean ± SE	0.020 ± 0.006	0.045 ± 0.005	0.050 ± 0.006	-0.004 ± 0.005
Range				
Percent Change Baseline to Cycle 26 (2-year)	n = 43	n = 48	n = 45	n = 56
Mean ± SE	1.86 ± 0.58	4.08 ± 0.44	4.90 ± 0.60	-0.33 ± 0.53
Range				
p-value	0.031	0.0001	0.0001	

p-value vs. placebo; *Completer = patient who completed the study and contributed Cycle 26 data.

The secondary data show significant difference between all Alora doses vs. placebo at all both Cycle 13 (1-year) and Cycle 26 (2-year) endpoints examined. The treatment effect observed in the completer analysis is similar to that of the ITT analysis.

Comment: As discussed above, the data base included baseline BMD, Cycle 13 BMD, and Exit BMD, but not Cycle 26 BMD. The Cycle 26 BMD data were derived.

C. Efficacy Conclusions

This study compared the effect of three doses of estrogen to placebo on the percent change in LS bone mineral density over a 2-year period in postmenopausal women. All Alora doses tested were found to have statistically significant greater mean percent changes in LS BMDs from baseline to endpoint. This study, however, had several short-comings in design and execution. First, greater than 20% of the patients enrolled would not be considered to be at risk for developing osteoporosis based on a screening BMI ≥ 30 kg/m^2 and T score > -1.0. Second, a number of patients were randomized into the trial who did not meet inclusion/exclusion criteria. For example, fourteen patients were randomized who had vertebral deformities at the time of screening — this would have interfered with accurate BMD measurements. Third, many patients in the study were using herbal and vitamin supplements that may have affected bone metabolism, such as vitamins D and K. And there is no evidence that the contents of these supplements were determined.

As a class, estrogens effectively decrease bone turnover and increase BMD in postmenopausal women. Because estrogen treatment is associated with increased risk of breast cancer, endometrial cancer and venous thrombosis, companies have attempted to identify the 'lowest effective dose'. Other low-dose estrogens have been approved for the prevention of postmenopausal osteoporosis. There is no reason to believe that similar doses of Alora should be less efficacious. The limitations in the study design and execution notwithstanding, subgroup analyses (BMI, time from hysterectomy, previous estrogen use, etc) performed by the Biometrics Reviewer shows that the efficacy results across subgroups are similar to the LOC analysis for the ITT population as a whole.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

In general, safety monitoring for this study was appropriate. The adverse events reported in this 2-year trial were consistent with estrogens as a class with the exception of skin reactions. Skin reactions were reported in > 50% of the patients treated with the Alora transdermal system and were responsible for early withdrawal of 7.9 to 10.1% of estrogen treated patients but no placebo treated patients.

B. Description of Patient Exposure

Three-hundred and fifty-five (355) patients were randomized to the study. Safety analyses included all subjects who received at least one dose of study drug. The mean duration of exposure was 495.6 days (median 722, range [redacted]. All safety variables were summarized in tabular form at each visit for each treatment group.

C. Methods and Specific Findings of Safety Review

Watson has reported the safety results by individual patient and by treatment group. Individual patient data listings are provided in an appendix of the NDA and in the electronic data base. Adverse Events (AEs) are listed by COSTART terms in both the appendix and electronic data bases for all patients, however, Case Report Forms are available for a limited number (22.8%) of patients and are in the electronic data set.

The safety data were reviewed focusing on those AEs that are associated with estrogen use. All serious and unexpected AEs will be outlined. Concomitant medications were reviewed for imbalances among treatment groups.

Safety Assessments

The safety monitoring schedule is as found in the protocol description and included annual mammograms, adverse events monitoring, coagulation factors, carbohydrate metabolism, lipid profile, and other laboratory determinations, and physical examinations. Mammograms were performed at screening and at the Cycle 13 and Cycle 26 (or exit) visits.

Adverse Events

Adverse events during treatment included adverse events which occurred up to 24 hours after the last dose of study drug. Adverse events were reported for a total of 247 patients (92%) in the 3 estradiol treatment groups and for 82 (94%) patients in the placebo group. Most adverse events (94%) were mild or moderate in severity. The majority of adverse events (70%) were considered doubtfully related to study drug by the investigator.

Deaths– Two subjects (Subject 517720 and 5193113), both in the 0.025 mg/day treatment group, reported serious adverse events that led to death. Both events occurred post treatment. Subject 5177120 had liver carcinoma that began 307 days after the start of study drug. Subject 5193113 had a myocardial infarction 673 days after the start of study drug.

Other Serious Adverse Events– Thirty-two (32) subjects (0.025 mg/d – 6; 0.050 mg/d – 6; 0.075 mg/d – 11; and placebo – 9) reported other serious adverse events during the study. Information of the 6 subjects who prematurely terminated because of serious adverse events is summarized in the following table. All subjects discontinued use of study medication.

Serious Adverse Events					
Subject No. (Age)	Days to onset	Preferred term	Investigator term	Severity	Outcome
Estradiol 0.025 mg/day					
14691176 (50)	38	Breast carcinoma	Metastatic breast cancer/stomach cancer	Moderate	Ongoing
	38	Stomach carcinoma	stomach cancer	Moderate	Ongoing
Estradiol 0.075 mg/day					
39051152 (57)	43	Hernia	Right femoral hernia	Severe	Recovered
	65	Hernia	Right femoral hernia exploratory surgery	Severe	Recovered
	75	Thrombosis	Left DVT of leg	Severe	Ongoing
41201133 (57)	563	Carcinoma	Metastatic carcinoma-bone, lungs, liver	Severe	Ongoing
51961075 (56)	386	Breast carcinoma	Carcinoma of left breast	Severe	Recovered
Placebo					
39041284 (48)	15	Cardiomyopathy	Cardiomyopathy of presumed viral etiology	Severe	Recovered
39231016 (59)	485	Spontaneous fracture bone	Fracture right forearm	Severe	Recovered
	485	Spontaneous fracture bone	Fracture right leg	Severe	Ongoing

The incidence of neoplasm-related adverse events are summarized in the following table:

Neoplasm Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Carcinoma	0	0	0	0	1	1.1	0	0	1	0.3
Carcinoma Breast	1	1.1	0	0	1	1.1	0	0	2	0.6
Carcinoma GI	1	1.1	1	1.1	0	0	0	0	2	0.6
Carcinoma Skin	0	0	1	1.1	1	1.1	1	1.1	3	0.8
Neoplasm	1	1.1	0	0	1	1.1	0	0	2	0.6
Neoplasm Breast	3	3.4	5	5.6	1	1.1	6	6.9	15	4.2
Neoplasm Skin	2	2.2	0	0	1	1.1	1	1.1	4	1.1
Neoplasm Urogenital	0	0	1	1.1	0	0	1	1.1	2	0.6
Nodule Skin	1	1.1	1	1.1	0	0	0	0	2	0.6

The most commonly reported neoplasm-related AE was breast neoplasm. The highest percentage was in the placebo group and the lowest percentage was in the 0.075 mg estrogen group, demonstrating no estrogen-related increase in the incidence of breast neoplasm in this study.

Adverse Events leading to premature withdrawal – Fifty-two (52) subjects had adverse events that led to premature withdrawal from the study. The adverse events that were the most frequent reasons for premature termination were application-site reactions (6.8%) and breast pain (1.7%). Twenty-four (24) subjects (estradiol 0.025 mg/day – 7 subjects [7.9%]; 0.050 mg/day – 8 subjects [8.9%]; 0.075 mg/day – 9 subjects [10.1%]; and placebo – 0 subjects) discontinued because of application-site reactions. Six subjects (estradiol 0.025 mg/day – 3 subjects [3.4%]; 0.050 mg/day – 1 subject [1.1%]; 0.075 mg/day – 2 subjects [2.2%]; and placebo – 0 subjects) discontinued because of breast pain. All other adverse events as reasons for premature termination were reported by 1 or 2 subjects per adverse event.

Adverse Events not leading to premature withdrawal – Twenty-eight (28) subjects reported 41 serious adverse events that did not lead to premature termination (estradiol 0.025 mg/day – 7 subjects; 0.050 mg/day – 6 subjects; 0.075 mg/day – 8 subjects; and placebo – 7 subjects).

Incidence of Adverse Events – Adverse events reported in ≥ 5% of patients in any group are reported in the following table. The 5% level is consistent with the current label.

Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Application Site Reaction	47	52.8	51	56.7	49	55.1	51	58.6	198	55.8
Systemic Reactions										
Pain Breast	13	14.6	16	17.8	31	34.8	7	8.0	67	18.9
Respiratory Infection	22	24.7	22	24.4	19	21.3	23	26.4	86	24.2
Arthralgia	5	5.6	10	11.1	11	12.4	12	13.8	38	10.7
Flu Syndrome	8	9.0	12	13.3	97	10.1	9	10.3	38	10.7
Pain Back	5	5.6	3	3.3	6	7.9	5	5.7	20	5.6
Breast Enlargement	1	1.1	2	2.2	6	6.7	3	3.4	12	3.4
Hypertension	3	3.4	3	3.3	6	6.7	3	3.4	15	4.2
Pain	9	10.1	5	5.6	6	6.7	11	12.6	31	8.7
Pruitus	2	2.2	1	1.1	6	6.7	4	4.6	13	3.7
Sinusitis	9	10.1	11	12.2	6	6.7	16	18.4	42	11.8
Headache	10	11.2	8	8.9	5	5.6	11	12.6	34	9.6
Myalgia	3	3.4	2	2.2	5	5.6	4	4.6	14	3.9

Comment: Although the incidence of application site reactions was similar among treatment groups, the severity of the reaction was classified as moderate for more patients in the estrogen treated groups (21.3%, 0.025 mg; 31.4%, 0.050 mg; and 34.7%, 0.075 mg) compared to the placebo group (9.8%). The incidence of breast pain is known to increase in a dose dependent fashion. The increased incidence of hypertension with the higher estrogen dose is also consistent with current labeling for estrogens.

Estrogen Associated Adverse Events – Other AEs known to be associated with estrogen use are summarized in the following table:

Estrogen Associated Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Edema	4	4.5	6	6.7	6	6.9	6	6.9	22	6.2
Weight Increase	3	3.4	2	2.2	5	5.7	6	6.9	16	4.5
Migraine	6	6.7	2	2.2	0	0	2	2.3	10	2.8
Fracture	1	1.1	3	3.3	0	0	7	8.0	11	3.1
All Psychiatric Disorders*	8	9.0	20	22.2	7	8.0	24	27..6	59	16.6
Hot Flushes (Vasodilation)	6	6.7	2	2.2	1	1.1	13	14.9	22	6.2
Thrombosis	0	0	0	0	1	1.1	0	0	1	0.3

*Summary of all Psychiatric Disorders Reported (anxiety, nervousness, emotional liability, insomnia, somnolence, dream abnormalities, depression, confusion)

Comment: All fractures were recorded as 'spontaneous'. A CRF was available for one of these patients. This patient was recorded to have sustained both an arm and leg fracture as a result of a motor vehicle accident. Given the non-specificity of the data recorded, the fracture data is of doubtful use.

Clinical experience has demonstrated that the incidence of hot flushes decreases an increased time from menopause. Therefore, the higher incidence of vasodilation in the placebo group compared to estrogen treatment groups is somewhat unexpected given the time from surgery (and likely menopause) for the majority of patients.

Summary of Adverse Events Reported

Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Number of Patients Reporting an Adverse Event	n	%	n	%	n	%	n	%	n	%
All Adverse Events	82	92.1	83	92.2	82	92.1	82	92.1	329	92.7
Serious Adverse Events	8	9.0	6	6.7	11	12.4	9	10.1	34	9.6
Application-Site Reaction Adverse Events	47	52.8	51	56.7	49	55.1	51	58.6	198	55.8
Adverse Events as Reasons for Premature Termination	14	15.7	12	13.3	20	22.5	6	6.9	52	14.6

Concomitant Medications

Concomitant medications by drug class for each treatment group were provided in tabular form. Medications started during the study were not reported separately but were included in the list of medications used by individual patients. Medications started in response to AEs events were reported in tabular form by drug class.

Comment: In general, there were no clinically significant imbalances in the concomitant medications among the treatment groups. Approximately 50% of patients used some form of vitamin supplement. As discussed in the Study Medication section the components of these supplements was not well described. More patients receiving estrogen treatment (all doses) than placebo required corticosteroids (dermatological preparations). This is consistent with the higher incidence of premature termination in these treatment groups.

Clinical Laboratory Evaluation

Hematology and clinical chemistry data, including serum lipid profile and carbohydrate metabolism parameters, were collected at screening and after cycles 7, 13, 20, and 26. Parameters that were followed included means and shifts and grade changes at each time point.

For changes from baseline in mean laboratory values, there were no significant changes in hematology or chemistry values. For hematology, this included hemoglobin, hematocrit, RBC, WBC and platelet counts. For serum chemistries, values included sodium, potassium, bicarbonate, chloride, and creatinine. For liver function tests, values included alkaline phosphatase, GGTP, AST, ALT and total bilirubin. Other tests include calcium, albumin, and phosphorus.

The number of patients with laboratory value shifts from normal (at baseline) to abnormal (high or low) post-baseline are generally similar among the treatment groups. Those shift frequencies that occurred in ≥ 5% of the patients are summarized in the following table:

Laboratory Value Shifts at exit by Treatment Group	Estradiol 0.025 mg/day N = 89 N*= 61		Estradiol 0.050 mg/day N = 90 N*= 72		Estradiol 0.075 mg/day N = 87 N*= 65		Placebo N = 87 N*= 75		Normal Range
Number of patients with shifts from normal to high or low	n	%	n	%	n	%	n	%	
Chloride (mEq/L) high	4	6.6	3	4.2	1	1.5	0	0	9.5-108 meq/l
GGTP (IU/L) high	1	1.6	2	2.8	7	10.8	3	4.0	0-45 IU/l
Phosphorus (mg/dl) high	4	6.6	2	2.8	4	6.2	7	9.3	2.5-4.5 mg/dl
PT (sec) low	30	50.8	40	56.3	33	53.2	35	50.0	10.0-12.5 sec
PTT (sec) low	6	10.2	9	12.7	6	9.7	10	14.3	24.0-36.0 sec
HBA_{1c} (%) high	4	6.7	2	2.8	5	7.8	5	6.8	< 6.5%
Cholesterol (mg/dl) high	5	8.2	5	6.9	7	10.8	1	1.3	<200 mg/dl
LDL (mg/dl) high	5	8.2	6	8.3	5	7.7	4	5.3	<130 mg/dl
Triglycerides (mg/dl) high	8	13.1	2	2.8	1	1.5	5	6.7	<200 mg/dl

N*= number of patients contributing data at time point

Comment: None of these results is clearly related to estrogen use. The increase in GGTP was seen with the highest dose of estrogen — the clinical significance of this is unclear given that transdermal delivery negates the first pass effect seen with oral estrogens. Increases in lipid values are difficult to interpret because the exclusion of patients with lipid abnormalities was changed as an addendum to the protocol. Since it is not clear whether these changes are related to estrogen use or to changes in concomitant medications, clinical significance can not be defined.

Vital Signs

Summary statistics were provided for blood pressure and heart rate. As noted in the summary of adverse events, hypertension was seen in the 0.075 mg/day estrogen treatment group. No other abnormalities were reported among the groups.

Mammography

There were no clinically important changes in mammographic findings in any treatment group from baseline. From 17 to 21% of patients had abnormalities of the left breast and 17 to 19% of the right breast at screening. Of those patients with changes from baseline, most had a worsening of the mammogram results (Left: 0%, 0.025 mg; 8.5%, 0.050 mg; 3.7%, 0.075 mg; and 1.6%, placebo. Right: 4%, 0.025 mg; 6.8%, 0.050 mg; 1.9%, 0.075 mg; and 1.6%, placebo.) Those patients diagnosed with breast neoplasms are outlined above.

D. Summary of Safety Findings and Limitations of Data

The safety profile appears to be consistent with other marketed estrogens. The formulation was changed during the course of the trial. It appears that the formulation used for the study is not the formulation for which Watson is requesting approval. Although the supplemental NDA submission to DRUDP demonstrated bioequivalence of the new formulation the maximum exposure appears to be 96 hours. There are no studies for the new formulation in this NDA. Approximately one-half of the patients enrolled in the study experienced skin irritation from the patch. It would be concerning if the new formulation caused an increase in this adverse event. An additional limitation of the Alora transdermal system is that

VIII. Dosing, Regimen, and Administration Issues

IX. Use in Special Populations

Alora is indicated for use by postmenopausal women and therefore not indicated for use in males, children (a pediatric waiver was requested) or pregnant women.

The majority (86.5%) of the subjects in this study were white. Osteoporosis is generally a condition of thin, white or Asian women. There is insufficient clinical information available to make recommendations for other populations.

The safety and effectiveness in geriatric patients (over age 65) have not been established (current labeling). This is concerning since estrogens are prescribed to many patients in this age group for prevent and treatment of osteoporosis. While some patients enrolled in this study were ≥ 65 years of age, the study was not designed to specifically address safety and efficacy in this population.

X. Conclusions and Recommendations

A. Conclusions

This 2-year study conducted by Watson Laboratories demonstrates that 0.025, 0.05, and 0.75 ug/day of transdermal estrogen increase LS BMD in a dose-dependent and by a statistically significantly greater extent than placebo in postmenopausal women without uteri. The safety profile of Alora appears to be similar to other estrogens.

B. Recommendations

Approval pending agreement with Watson on final product labeling.

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XI. Appendix (Proposed Labeling)

Annotated version of proposed labeling changes with Reviewer's comments.

Estradiol Matrix
Transdermal Delivery System

Annotated Package Insert

May 9, 2001

Watson Laboratories Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108 USA

Note: Labeling changes from the Medical reviewer are incorporated into the body of the text. When indicated, comments related to the changes appear in text boxes and are not to be incorporated into the label.

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Labeling

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/s/

Patricia Beaston-Wimmer
11/2/01 04:39:39 PM
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Eric Colman
11/7/01 11:40:46 AM
MEDICAL OFFICER

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